REMARKS

Claims 1 to 17, 29 and 35 are currently pending on entry of the amendments above. Claims 18 to 28, 30 to 34 and 36 to 49 have been cancelled without prejudice or disclaimer and Applicants reserve the right to pursue the subject matter of these claims in related applications.

No new matter has been introduced on entry of this amendment.

Restriction Requirement

The Examiner has required an election under 35 U.S.C. § 121 of one of the following groups:

I. Claims 1-16, drawn to a method of treating or preventing an inflammatory disease or disorder comprising administering an antibody that binds TNF-γ-β, classified in Class 424, subclass 130.1.

II. Claims 17-28, drawn to a method of treating or preventing an autoimmune disease or disorder comprising administering an antibody that binds TNF-γ-β, classified in Class 424, subclass 130.1.

III. Claims 29-34 drawn to a method of treating or preventing GVHD comprising administering an antibody that binds TNF-γ-β, classified in Class 424, subclass 130.1.

IV. Claims 35-49, drawn to a method of killing a cell of hematopoietic origin comprising administering TNF-γ-β, classified in Class 514, subclass 12.

See, Paper No. 20030920, page 2. The Examiner contends that the inventions are distinct, each from the other. Applicants respectfully disagree and traverse.

In order to be fully responsive, Applicants provisionally elect, *with traverse*, the subject matter of group I as represented by originally filed claims 1-16, and drawn to a method of treating or preventing an inflammatory disease or disorder comprising administering an antibody that binds TNF-γ-β, for further prosecution. Applicants reserve

the right to file one or more divisional applications directed to non-elected inventions should the restriction requirement be made final. Additionally, should the present restriction requirement be made final, Applicants retain the right to petition from the restriction requirement under 37 C.F.R. § 1.144.

Applicants point out that claims 18 to 28, 30 to 34, and 36 to 49 have been canceled and that no new claims have been added.

Applicants respectfully traverse and request the withdrawal of the Restriction Requirement. As a threshold matter, Applicants point out that MPEP § 803 lists the criteria for a proper restriction requirement:

> Under the statute an application may properly be required to be restricted to one of two or more claimed inventions only if they are able to support separate patents and they are either independent (MPEP § 806.04 – § 806.04(i)) or distinct (MPEP § 806.05 – § 806.05(i)).
>
> If the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions.

Thus, even assuming, *arguendo*, that the groups listed by the Examiner represented distinct or independent inventions, restriction remains improper unless it can be shown that the search and examination of both groups would entail a "serious burden." *See* M.P.E.P. § 803.

In the present situation, no such showing has been made. In analyzing the instant claims the Examiner has restricted the subject matter of each of the groups described in Paper No. 20030920. The Examiner alleges that the subject matter of each of the four described group is distinct from that of every other group. In support of this determination the Examiner has made a number of statements concerning the nature of inflammation,

autoimmunity, graft-versus-host disease and hematopoietic cells. Applicants respectfully traverse these allegations.

In the first instance, the Examiner alleges that "inflammation is a nonimmune host defense that uses phagocytic cells (neutrophils, monocytes, and macrophages), cells that release inflammatory mediators (basophils, mast cells, and eosinophils), and natural killer cells." *See*, Paper No. 20030920, page 2. Applicants disagree and traverse.

As stated by the Examiner, inflammation is a host defense, which results from the inflammatory response, which occurs when a tissue is exposed to any one of a number of noxious stimuli including, for example, bacterial infections. *See*, e.g., Exhibit A, Janeway, C.A. and Travers, P. 'IMMUNOBIOLOGY – The Immune System in Health and Disease', Garland Publishing Inc., N.Y. and London, at pages 1:30 to 31 (1994). As described by the authors, the initial inflammatory response is characterized by certain specific events including blood vessel dilation, local increase in vessel stickiness for passing immune cells, and increased vessel permeability to fluid and immune cells. While the first cells involved in the inflammatory response are non-specific 'inflammatory cells' such as monocytes and neutrophils, later recruitment and activation of immune cells (T cells) is believed necessary to sustain chronic inflammation. Therefore, contrary to the allegation made by the Examiner, inflammation is not a "nonimmune host defense," but rather a process long known to involve cells of the immune system.

The Examiner further alleges that "[b]ecause these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper." *See*, Paper No. 20030920 at page 3. Applicants respectfully disagree and traverse.

Applicants contend that in light of the above comments relating to inflammation, autoimmunity and GVHD, and the evidence submitted herewith in Exhibits A-C, it is clear that the subject matter of groups I-III identified by the Examiner are closely related, as each pertains to the regulation of T-cell activity in order to control disease pathogenesis. Furthermore, Applicants point out that the subject matter of groups I, II and III are classified in class 424, subclass 130.1 and therefore these groups have not "acquired a separate status in the art as shown by their different classification" as alleged by the Examiner.

Groups I-III are directed to methods of treating or preventing immune diseases using antibodies that bind TNF-γ-β; therefore a search directed to the antibodies would likely reveal the various immune diseases that can be treated by the antibodies, including those of groups I, II and III. Furthermore, since a search of the subject matter of groups I, II and III would largely, if not entirely, overlap; and since the subject matter of each of these groups is classified in the same class and subclass, the search and examination of all these groups would not entail a serious burden. Therefore, Applicants respectfully suggest that the present restriction as it pertains to groups I-III is improper and request that it be withdrawn.

Furthermore, even though groups I-III and group IV are separately classified, Applicants nonetheless submit that a search of the claims of group I-III would also provide useful information for the claims of group IV, while a search of the claims of group IV would provide useful information for the claims of groups I-III. Indeed, since groups I-III are directed to methods of treatment of disease by regulation of hematopoietic cell function using antibodies that bind TNF-γ-β, and group IV is directed to methods of

killing hematopoietic cells using TNF-γ-β polypeptides, a search of both of these groups would largely, if not entirely, overlap.

For example, in many if not most publications disclosing the use of a polypeptide in treating or ameliorating a disease, a polynucleotide is described which encodes that polypeptide. Furthermore, in many if not most publications disclosing altered expression of a polypeptide in a disease, a suggestion is made that regulation of the function and/or expression of that polypeptide may be useful in treating and/or ameliorating that disease. Accordingly, since the searches for diseases overlap, and the searches for polynucleotides and polypeptides overlap, the search and examination of all groups of the instant application would not entail a serious burden.

Accordingly, in view of M.P.E.P. § 803, the claims of all groups I-IV should be searched and examined in the present application. Applicants therefore respectfully request that the restriction requirement under 35 U.S.C. § 121 be reconsidered and withdrawn, and that the instant claims be examined in one application.

Species Elections

The Examiner has alleged that "[t]his application contains claims directed to the following patentably distinct species of the claimed invention: monoclonal antibody, human antibody, humanized antibody," and required an election under 35 U.S.C. § 121 of a single disclosed species for prosecution on the merits, "to which the claims shall be restricted if no generic claim is finally held allowable." *See*, Paper No. 20030920 at pages 3-7. Applicants respectfully disagree and traverse.

In order to be fully responsive, Applicants provisionally elect, *with traverse*, the method of group I, wherein the antibody is monoclonal. Applicants reserve the right to

file one or more divisional applications directed to non-elected species should the requirement for election be made final and no generic claims found allowable. Additionally, should the present requirement for an election be made final, Applicants retain the right to petition from the restriction requirement under 37 C.F.R. § 1.144.

Applicants respectfully traverse and request the withdrawal of the requirement to elect a single species for prosecution. Preliminarily, Applicants point out that at least claims 1, 3, 11 and 13 of group I, are generic to the instant provisionally elected subject matter. Accordingly, the search of each generic claim will entail a search for prior art methods of treating or preventing inflammatory diseases or disorders comprising administering to an animal in which such treatment or prevention is desired an antibody or fragment thereof that specifically binds TNF-gamma-beta protein in an amount effective to treat or prevent the inflammatory disease or disorder. It is necessary to perform this search no matter which species are elected because claim 1 is a generic linking claim for each of the species identified by the Examiner in Paper No. 20030920.

Applicants further point out that MPEP § 806.04(d) states:

> Once a claim that is determined to be generic is allowed, all of the claims drawn to species in addition to the elected species which include all the limitations of the generic claim will ordinarily be obviously allowable in view of the allowance of the generic claim, since the additional species will depend thereon or otherwise include all of the limitations thereof.

Accordingly, the search of the method of claim 1 is all that is necessary to allow examination of all the species, elected and non-elected. This is because the search of the method of generic linking claim 1 is a broader search than the search for any one of the individual species. If no art is found for claim 1, then all species should be allowable over the prior art, because each of the narrower claims contain species containing all the

limitations of claim 1. If claim 1, is novel, so will all the species be novel (*see*, MPEP § 806.04(d)). Accordingly, Applicants respectfully request that instant requirement for election of species within Group I be withdrawn and the instant claims be examined in one application.

The Examiner has further alleged that "[t]his application contains claims directed to the following patentably distinct species of the claimed invention: the species of claim 7, 8, 9, or 10," and required an election under 35 U.S.C. § 121 of a single disclosed species for prosecution on the merits, "to which the claims shall be restricted if no generic claim is finally held to be allowable." *See*, Paper No. 20030920 at pages 3-7. Applicants respectfully disagree and traverse.

In order to be fully responsive, Applicants provisionally elect, *with traverse*, the method of group I, wherein the inflammatory disease or disorder is inflammatory bowel disease. Applicants reserve the right to file one or more divisional applications directed to non-elected species should the requirement for election be made final and no generic claims found allowable. Additionally, should the present requirement for an election be made final, Applicants retain the right to petition from the restriction requirement under 37 C.F.R. § 1.144.

Applicants respectfully traverse and request the withdrawal of the requirement to elect a single species for prosecution. As discussed above, at least claims 1 and 3 of group I, are generic to the instant provisionally elected subject matter. Accordingly, the search of each generic claim 1 will entail a search for prior art methods of treating or preventing inflammatory diseases or disorders comprising administering to an animal in which such treatment or prevention is desired an antibody or fragment thereof that specifically binds TNF-gamma-beta protein in an amount effective to treat or prevent the inflammatory

disease or disorder. It is necessary to perform this search no matter which species are elected because claim 1 is a generic linking claim for each of the species identified by the Examiner in Paper No. 20030920.

Again, Applicants point out that "[o]nce a claim that is determined to be generic is allowed, all of the claims drawn to species in addition to the elected species which include all the limitations of the generic claim will ordinarily be obviously allowable in view of the allowance of the generic claim." *See*, MPEP § 806.04(d).

Accordingly, the search of the method of claim 1 is all that is necessary to allow examination of all the species, elected and non-elected. This is because the search of the method of generic linking claim 1 is a broader search than the search for any one of the individual species. If no art is found for claim 1, then all species should be allowable over the prior art, because each of the narrower claims contain species containing all the limitations of claim 1. If claim 1, is novel, so will all the species be novel (*see*, MPEP § 806.04(d)). Accordingly, Applicants respectfully request that instant requirement for election of species within Group I be withdrawn and the instant claims be examined in one application.

In accordance with the requirement that Applicants identify claims believed corresponding to the elected subject matter, Applicants confirm that they have provisionally elected, *with traverse*, the method of the claimed invention, wherein the antibody is monoclonal and the inflammatory disease or disorder is inflammatory bowel disease, for further prosecution. Applicants understand the provisionally elected subject matter to be read upon by pending claims 1-4, 7 and 11-14.

Applicants respectfully request that the above-made amendments and remarks be entered and made of record in the file history of the instant application.

Conclusion

In view of the foregoing remarks, applicants believe that this application is now in condition for substantive examination. The Examiner is invited to call the undersigned at the phone number provided below if any further action by applicant would expedite the examination of this application.

Finally, if there are any fees due in connection with the filing of this paper, please charge the fees to our Deposit Account No. 08-3425. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Dated: October 23, 2003

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Enclosures
KKH/LJH/BM/lcc

EXHIBIT A

IMMUNOBIOLOGY

THE IMMUNE SYSTEM IN HEALTH AND DISEASE

Charles A. Janeway, Jr.
Yale University Medical School

■

Paul Travers
Birkbeck College, London University

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BIOLOGY
LIMITED ■

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Many microorganisms, especially bacteria, have conserved surface molecules that are recognized by phagocytic cells, which play an important part in the early elimination of infection as well as serving as professional antigen-presenting cells and thereby inducing the later adaptive immune responses. These phagocytic cells include macrophages and neutrophils, which not only ingest and destroy extracellular microorganisms, and in particular bacteria, but are also important in recruiting other cells and molecules of the immune system by releasing chemicals that have effects collectively called inflammation.

1-19 Infection often triggers an inflammatory response.

The term **inflammation** is purely descriptive and was originally defined by the four Latin words *dolor*, *rubor*, *calor*, and *tumor*, meaning pain, redness, heat, and swelling. These changes result from changes in the local blood vessels, leading to their dilation, increased permeability, and increased stickiness for passing leukocytes and lymphocytes. The increased blood flow accounts for the heat and redness, while the leakage of cells and fluids into the tissue and their local actions account for the pain and swelling. The main cell types seen in inflammatory responses are polymorphonuclear neutrophilic leukocytes together with macrophages and their precursor monocytes; these are therefore known as **inflammatory cells**. Lymphocytes, as well as small numbers of eosinophils and basophils, also accumulate at sites of inflammation and, when extreme vascular leakage occurs, red blood cells may also occasionally be found. Inflammatory responses can be triggered directly by pathogens, especially bacteria, early in infection, and may be sustained later by antibodies and by T cells, which release inflammatory factors. In the early phase of an infection, inflammatory responses are important in attracting nonspecific inflammatory cells such as monocytes and neutrophils to the site of an infection. Later, the same changes attract effector lymphocytes, and

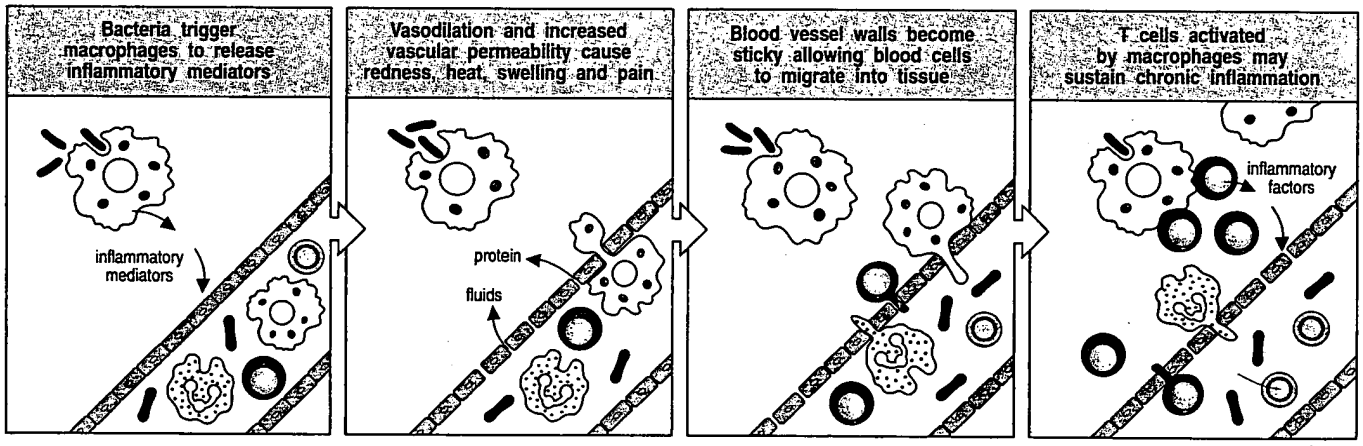

Fig. 1.32 Bacterial infection trigg rs an inflammatory r sponse. Macrophages encountering bacteria in the tissues are triggered to release chemicals that increase the permeability of blood vessels, allowing fluid and proteins to pass into the tissues. The stickiness of the endothelial cells of the blood vessels is also changed, so that cells adhere to the blood vessel wall and are able to crawl through it: macrophages and polymorphonuclear neutrophilic leukocytes (neutrophils) are shown here entering the tissue from a blood vessel. The accumulation of fluid and cells at the site of infection causes the swelling, heat, and pain that are collectively known as inflammation. Macrophages and neutrophils are the principal inflammatory cells. Later in an immune response, activated lymphocytes also contribute to inflammation.

the increased permeability of the blood vessels allows the passage of antibodies into infected tissues (Fig. 1.32).

Many different stimuli can trigger inflammatory responses. Physical injury from wounds or burns releases proteins from tissues that trigger acute inflammatory reactions similar to those activated directly by bacteria. Chronic inflammatory processes are usually triggered by T cells, especially those that activate macrophages, as activated macrophages frequently cause local tissue damage through the release of mediators similar to those elicited by bacteria. Finally, some forms of acute inflammatory response are triggered by specific antibodies binding to antigen and activating the complement system, or interacting with accessory cells through their receptors for bound antibody molecules, as we shall see in the next section. The inflammatory response is a general term to describe both the gross and microscopic picture of local tissue infiltration by fluid and cells triggered in these different ways.

1-20 Specific recognition of pathogens by antibodies activates non-specific accessory cells.

Many microorganisms have evolved adaptations to their surface molecules that enable them to escape direct detection by any of the innate mechanisms we have described above. These microorganisms must be recognized by lymphocytes whose diverse receptors enable them to detect any pathogen and mount an adaptive immune response. The mechanisms whereby microorganisms are then destroyed, however, are essentially the same for the innate and adaptive arms of the immune response.

Thus, bacteria that resist direct binding by complement and are not bound by acute-phase proteins can become coated with specific antibodies. Once the antibodies have bound to the bacterium, they in turn recruit complement (see Fig. 1.22), as well as **accessory effector cells** that have receptors for bound antibody and complement molecules. These effector cells are the same as those that participate in innate immunity, and thus antibody, by flagging a pathogen as foreign, is able to overcome the ability of some pathogens to evade innate immune mechanisms. The accessory cells and the mechanisms whereby they eliminate pathogens are summarized in Fig. 1.33; we shall learn more about these cells when we discuss humoral immunity in Chapter 8.

Similarly, T cells recognize antigen specifically, but then trigger effector mechanisms that are not antigen specific. Specificity in cell-mediated immunity comes from the antigen-specific release of antigen-nonspecific effector molecules. Thus, killer CD8 T cells release their cytotoxic molecules only when they encounter an infected host cell, and inflammatory CD4 T cells activate only infected macrophages. Only in the case of B-cell activation by helper T cells is the target of T-cell action also antigen specific; however in this case, as we have just seen, the effector mechanism ultimately activated by the antibodies will not be antigen-specific. Thus, in both humoral and cell-mediated immunity, specificity derives from the clonally distributed receptors on antigen-specific lymphocytes, while effector function is mediated by cells and molecules that are not specific for antigen. This allows the same effector mechanisms to be used in response to a wide range of distinct pathogens.